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REVIEW

When therapeutic drugs lead to diabetes

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Abstract

Drug-induced diabetes mellitus is a growing problem in clinical practice. New, potent medications contribute to this problem in a population already at high risk of developing glucose disturbances because of poor lifestyle habits and high prevalence of being overweight/obese. The present review focuses on four important pharmacological classes: glucocorticoids; antipsychotics, especially second generation; antiretroviral therapies, which revolutionised the management of individuals with HIV; and immune checkpoint inhibitors, recently used for the immunotherapy of cancer. For each class, the prevalence of drug-induced diabetes will be evaluated, the most common clinical presentations will be described, the underlying mechanisms leading to hyperglycaemia will be briefly analysed, and some recommendations for appropriate monitoring and management will be proposed.

Keywords Antipsychotics · Antiretroviral therapy · Drug-induced diabetes · Glucocorticoids · Immune checkpoint inhibitors · Review · Secondary diabetes

Abbreviations

ART	Antiretroviral therapy
AT	Adipose tissue
CTLA-4	Cytotoxic T lymphocyte antigen-4
DKA	Diabetic ketoacidosis
GC	Glucocorticoid
GCIDM	GC-induced diabetes mellitus
GLP-1	Glucagon-like peptide-1
HT	Hydroxytryptamine
ICI	Immune checkpoint inhibitor
INSTI	Integrase strand transfer inhibitor
NNRTI	Non-nucleoside analogue reverse transcriptase inhibitor
NRTI	Nucleoside analogue reverse transcriptase inhibitor
PD-1	Programmed death-1
PDL-1	Programmed death-ligand-1
PI	Protease inhibitor
PYFU	Person-years of follow-up
SGA	Second-generation antipsychotic
UCP-1	Uncoupling protein-1

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Introduction

In clinical practice, commonly used drugs may interfere with glucose homeostasis and provoke impaired glucose tolerance, hyperglycaemia or new-onset diabetes mellitus, or may worsen glycaemic control in individuals with diabetes [1]. These adverse events occur especially in individuals with a predisposition due to their genetic background and/or unfavourable environment upon which the deleterious effects of the medications are superimposed. Pharmacogenomics can regulate the expression of genes involved in signalling pathways related to the pharmacokinetics or pharmacodynamics of drugs or the pathogenesis of diabetes, thus contributing to potential interindividual differences in drug-induced glucose

impairment [2]. Drug-induced diabetes is now recognised as a component of secondary diabetes.

Numerous pharmacological compounds can alter glucose homeostasis by different mechanisms: reduced tissue insulin sensitivity via intrinsic direct mechanisms; promotion of weight gain; and/or functionally impaired insulin secretion. Some also increase hepatic glucose production, induce acute pancreatitis or even exert direct cytotoxic effects on pancreatic beta cells (Table 1) (see review in [1]). The present concise narrative review will focus on four important pharmacological classes: glucocorticoids (GCs); antipsychotics; antiretroviral therapy (ART); and immune checkpoint inhibitors (ICIs). These drug classes were selected because of their increasing use in clinical practice and their potential risk for severe hyperglycaemia/diabetes. Other medications, such as statins, merit attention because they are widely used in individuals with or at risk of diabetes. A meta-analysis of 14 trials suggested a 9–33% higher risk of new-onset diabetes with statin use. However, any deterioration of glucose control is generally mild, including that occurring in individuals with diabetes. The underlying diabetogenic action of statins likely results from a complex interplay between pancreatic and extrapancreatic effects. Nevertheless, cardiovascular protection by statin treatment outweighs the risks associated with development of new-onset diabetes or modest deterioration of glucose control in individuals with diabetes [3].

Of note, transient reversible (sometimes severe) hyperglycaemia should be distinguished from true diabetes with sustained (but less severe) hyperglycaemia. High doses of GCs given for a short period may result in severe acute but reversible hyperglycaemia; low doses of GCs, antipsychotics and antiretrovirals given as long-term treatments may result in diabetes-related long-term complications. Drug-induced diabetes may be reversible if the medication is discontinued; however, it may be permanent, depending on the characteristics of the drug therapy (medication, dose, duration) or the patient's background profile (age, body weight, family history). Proposals for the medical surveillance and management of drug-induced diabetes are very similar to recommendations for other types of diabetes (especially type 2 diabetes), focusing on lifestyle (diet and exercise) and, if necessary, stepwise glucose-lowering treatment, usually starting with metformin. Only specific aspects relating to each drug class that differ from the classical management of individuals with diabetes will be discussed.

- Clinicians should be aware of the risk of new-onset diabetes or worsening of diabetes when prescribing some drugs, especially in individuals already at risk
- Focus should be on glucocorticoids, antiretroviral therapy, new-generation antipsychotics and immune checkpoint inhibitors
- Because of different underlying mechanisms, both prevention and treatment may differ between the four studied pharmacological groups
- Drug-induced weight gain (abdominal adiposity and 'adiposopathy') contributes to disturbances in glucose homeostasis
- Lifestyle (diet and exercise) recommendations should be reinforced in individuals who receive drugs that could lead to weight gain and diabetes
- Pharmacotherapy of drug-induced diabetes is similar to that of other forms of diabetes, with a stepwise approach from metformin to insulin if required

Glucocorticoids

GC-induced diabetes mellitus (GCIDM) has been recognised for over 60 years, with GCs being most often associated with the onset of acute hyperglycaemia or diabetes [4]. However, the diagnosis and treatment of GCIDM are surprisingly underevaluated by healthcare professionals and prospective studies comparing the effectiveness and safety of GC treatments are lacking.

Prevalence GCIDM is defined as an abnormal increase in blood glucose levels during GC use in individuals with or without a prior history of diabetes. Where diabetes is preexistent, exposure to exogenous GCs systematically worsens glucose homeostasis [5]. In the absence of preexisting diabetes, the prevalence of GCIDM varies from 2% in outpatient general practice medicine to 32% in individuals with an organ transplant or with rheumatoid arthritis [4]. However, the fact that some individuals treated with GCs remain free from diabetes suggests that GCIDM occurs in those who are vulnerable. The duration of treatment and the daily GC dose are key determinants of diabetes risk [6]. Besides, an individual's characteristics, similar to those predisposing to type 2 diabetes (i.e. higher BMI, older age, African American race, and a family history of diabetes), can predispose to GCIDM [7], as well as gestational diabetes or GC-induced hyperglycaemia [4].

Clinical presentation GCIDM usually occurs early during the course of GC exposure, yet sensitivity to GCs' efficacy and

side-effects is highly variable. Measurement of capillary or venous blood glucose is often sufficient to screen for GCIDM, yet fasting glucose shows poor sensitivity [6]. Continuous blood glucose monitoring has shown that hyperglycaemia occurs in the afternoon and evening [8], particularly with intermediate-acting GCs (prednisone, prednisolone, methylprednisolone) given as single morning doses (the most frequently prescribed regimen). A more useful criterion for the diagnosis of GCIDM is a blood glucose level >11.1 mmol/l at any time of the day. HbA_{1c} may be a suitable means of diagnosis in individuals treated for >2 months; fructosamine could represent a better alternative after short-term GC exposure [4]. Worsening of glucose control occurs within hours of GC initiation in individuals with diabetes, while the time to onset of hyperglycaemia in individuals without diabetes is highly variable [9].

GCs, commonly employed as the semi-synthetic presentation prednisolone (or its prodrug prednisone in some countries), are usually prescribed in two main patterns: short-term use of medium–high doses to treat a large range of inflammatory illnesses (whereby more than half of hospitalised individuals without known diabetes experience hyperglycaemia [9]); and long-term use at lower doses (e.g. <10 mg prednisolone/day) to attenuate chronic inflammatory disease progression or to prevent organ transplant rejection. These 'lower' doses are frequently higher than average endogenous GC production (~3 mg prednisolone a day). Interestingly, diabetic ketoacidosis (DKA) or hyperosmolar decompensations are very rare in GCIDM [9].

GC regimens other than oral prednisone/prednisolone are also used and differences in dose equivalence, anti-inflammatory activity and biological $t_{½}$ (Table 2) can influence therapeutic strategies. Locally injected (intra-articular, epidural) GCs are associated, although at a relatively lower rate, with disturbed blood glucose in individuals without previous diabetes, or with worsening glucose control in individuals with pre-existing diabetes [11, 12]. However, glycaemic response to intra-articular injections varies widely, depending on the number of joints injected and the type and dose of GC, and is an important consideration when estimating diabetes risk [12].

Pathophysiology/mechanisms As for type 2 diabetes, the mechanisms underlying GCIDM combine both insulin resistance and altered beta cell insulin secretion through effects on liver, skeletal muscle, adipose tissue (AT) and pancreatic beta cells (Fig. 1).

In the liver, GCs increase hepatic glucose production by gluconeogenesis induction. They activate enzymes and genes involved in glucose metabolism and potentiate other hormones, such as glucagon, that regulate glucose homeostasis while antagonising the metabolic action of insulin [13, 14]. In skeletal muscle, GCs reduce insulin sensitivity, thereby decreasing glucose uptake and inhibiting glycogen synthesis,

Table 1 Drug-induced hyperglycaemia and diabetes mellitus

Pharmacological classes	Main mechanisms	Characteristics
Drugs discussed in this review		
GCs	Increase in hepatic glucose production (gluconeogenesis) Interference with multiple glucoregulatory pathways	Dose-dependent, rapid effect
Antipsychotics	Body weight gain Direct effects on insulin signalling and secretion	Atypical (SGA> first generation) Hierarchy among SGA Dose-dependent
ART	Lipoatrophy, lipohypertrophy and insulin resistance	Reduced toxicity with newer compounds
ICIs	Immune destruction of beta cells	Partial similarities with type 1 diabetes Risk of DKA
Selected drugs not discussed in this review		
β-blockers	Impaired insulin release	Non-selective > β_1-selective, long-term effect
Diuretics	Impaired insulin release (via hypokalaemia) Increased insulin resistance	Dose-dependent, thiazides > loop diuretics, long-term effect
Calcineurin inhibitors	Reduced insulin secretion	Avoid in pancreas/beta cell transplantation
Sexual steroids	Increased insulin resistance	Mainly those with androgenic component
β_2-adrenoreceptor agonists	Increase hepatic glucose output	Systemic administration, dose-dependent
Somatostatin receptor agonists	Reduced insulin secretion	Rapid effect, mainly with pasireotide
Statins	Interference with multiple glucoregulatory pathways	Dose- and time-dependent effect
mTOR inhibitors	Interference with the insulin signalling pathway	Rapid and dose-dependent effect

mTOR, mechanistic target of rapamycin

Table 2 Characteristics of glucocorticoids commonly used in clinical practice

GC molecule	Equivalent dose (mg)[a]	Anti-inflammatory activity (relative to hydrocortisone)	Biological $t_{½}$ (h)
Hydrocortisone	20[b]	1	8–12
Prednisone	5	4	12–36
Prednisolone	5	4	12–36
Deflazacort	5	4	<12
Triamcinolone	4	5	12–36
Methylprednisolone	4	5	12–36
Dexamethasone	0.75	30	36–72
Betamethasone	0.6	25	36–72

Anti-inflammatory activity is expressed relative to that of hydrocortisone, which has been arbitrarily set to 1

[a] For a so-called equivalent dose, the hyperglycaemic effect appears almost comparable between the different GCs, yet few direct comparative studies are available [10]

[b] Twenty milligrams of hydrocortisone correspond to the endogenous daily production of cortisol

with subsequent hyperglycaemia [7]. GCs alter the expression and/or phosphorylation of major effectors of the insulin signalling pathway, leading to decreased GLUT4 expression at the plasma membrane [15]. The effects of GCs on AT are pleiotropic and contribute to disturbed glucose homeostasis. GCs promote exaggerated visceral AT expansion, associated with a higher risk of diabetes. This effect could involve complex and complementary mechanisms: (1) higher density

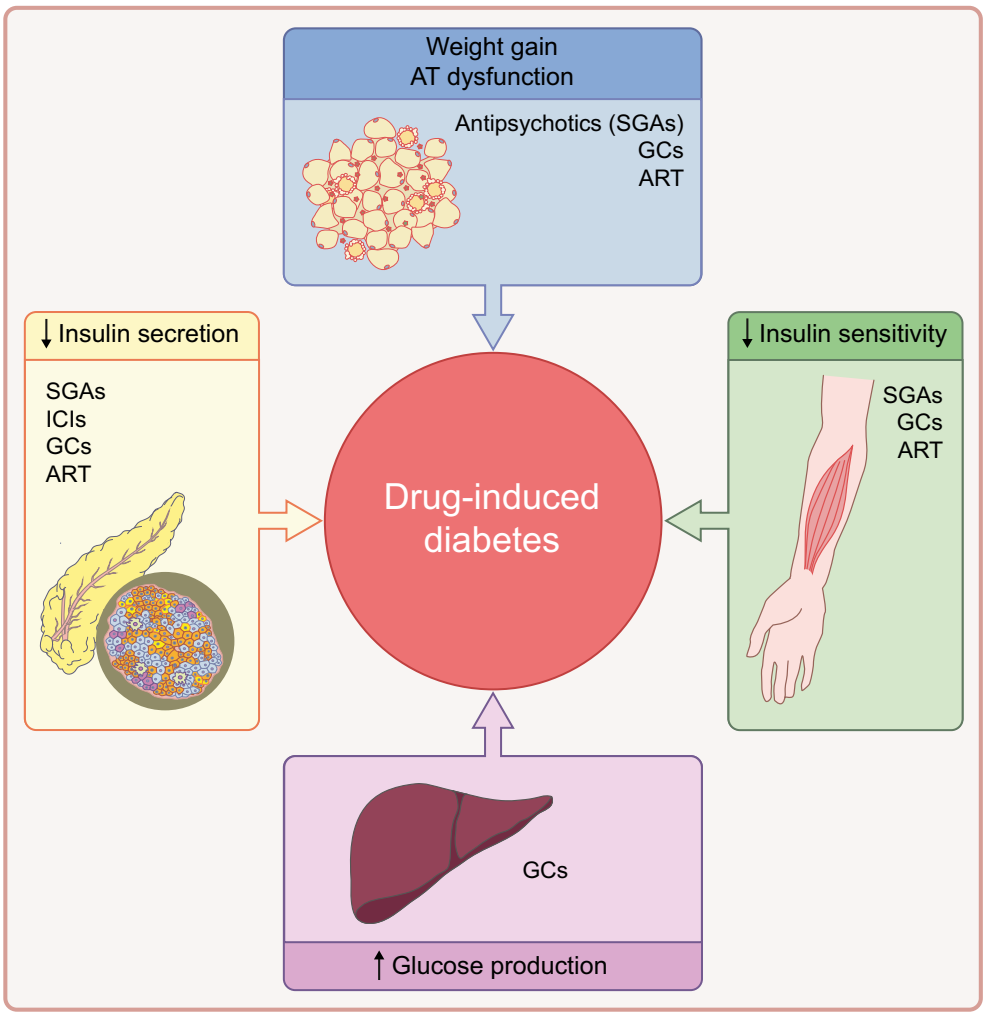

Fig. 1 Mechanisms leading to drug-induced hyperglycaemia for the four pharmacological classes considered in this review. AT dysfunction ('adiposopathy') also includes a proinflammatory state and an unhealthy fat distribution. For all indicated drugs, arrows indicate that they can induce diabetes mellitus either by promoting weight gain or adipose tissue dysfunction, and/or decrease insulin secretion, and/or reduce insulin sensitivity, and/or increase hepatic glucose production. This figure is available as a downloadable slide

of GC receptors in visceral AT vs other fat depots; (2) higher activity in visceral AT of the type 1 11β-hydroxysteroid dehydrogenase, which regenerates cortisol from cortisone (or prednisolone from prednisone), amplifying the local action of GC; and (3) the GC-dependent factor LIM domain only 3 (LMO3), which favours visceral fat accumulation [16]. Interestingly, while GCs promote adipocyte hypertrophy by increasing adipocyte differentiation and lipid storage, they also stimulate lipolysis through activation of hormone-sensitive lipase and catecholamine responsiveness [7]. These permissive effects on lipolysis increase plasma NEFA concentrations, possibly impairing insulin sensitivity and secretion. GCs also modulate the expression and secretion of adipokines, such as adiponectin, leptin and resistin [17], with subsequent alterations in insulin sensitivity. We recently showed that the adipocyte GC receptor plays a crucial role in modulating AT expansion and whole-body glucose homeostasis [18].

In pancreatic beta cells, chronic exposure to high doses of GCs inhibits the production and secretion of insulin [19]. However, even if GCIDM reflects the inability of beta cells to overcome GC-induced insulin resistance, some recent data from our group suggest that GCs can promote the synthesis and secretion of a circulating factor that induces beta cell development and insulin synthesis [20].

Medical surveillance and management There are no consensus guidelines or established therapeutic goals for the management of individuals with GCIDM [4, 9]. It is important to differentiate between temporary and indefinite treatment with GCs. The clinical presentation and type, dose and frequency of GC administration must be considered when determining appropriate care. In diabetic individuals treated with insulin, it is recommended that insulin doses should be adjusted to prevent excessive disturbance in glucose control. In those with pre-existing type 2 diabetes, more intensive self-monitoring of glucose levels is recommended when therapy with GCs is initiated.

The choice of glucose-lowering drug depends on its potential advantages and disadvantages and on the type and schedule of the GC [4, 9]. For mild hyperglycaemia, drugs that increase insulin sensitivity (e.g. metformin) are often considered first [4, 9]. Sulfonylureas, which lower blood glucose by stimulating insulin secretion in a glucose-independent manner, have also proved effective [21] but increase the risk of hypoglycaemia, especially when doses of GCs are decreased. Incretin mimetics, such as dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, might be useful in individuals receiving high doses of prednisolone [22]. Of note, exenatide has been shown to prevent prednisone-induced impaired glucose tolerance and islet-cell dysfunction in healthy individuals [23].

Insulin therapy is recommended when hyperglycaemia is severe. It combines efficacy, safety, immediate onset of action, unlimited hypoglycaemic power, and easy titration according to blood glucose measurements [9]. Because of the relatively short-term effects of most GCs, a morning injection of a basal insulin is preferable. When possible, reducing the dose or discontinuing the GC can improve insulin resistance and glycaemic control. It is crucial to avoid the risk of hypoglycaemia during the phase of GC dose decrease [24]. Notably, some individuals with GCIDM do not recover their baseline blood glucose level after stopping GCs.

Antipsychotics

Antipsychotics are divided into two broad categories (Table 3). The phenothiazines and butyrophenones are first-generation or typical antipsychotics. Their main antipsychotic activity arises from antagonism of dopamine D_2 receptors in the brain, possibly resulting in extrapyramidal movement disorders and hyperprolactinaemia. Second-generation antipsychotics (SGAs) (atypical antipsychotics) were developed to minimise these adverse effects. They have a much lower affinity for D_2 receptors and exert their antipsychotic effect

Table 3 Mechanism of action and adverse effects of antipsychotics

Class	Drugs	Molecular mechanisms	Adverse effects
First generation (typical)	Phenothiazine derivatives (e.g. chlorpromazine) Butyrophenone derivatives (e.g. haloperidol)	Mainly dopaminergic D_2-receptor antagonism	Extrapyramidal symptoms Hyperprolactinaemia Weight gain, with low risk of DM
Second generation (atypical)	Clozapine Olanzapine Risperidone Quetiapine Aripiprazole Ziprasidone	Mainly 5-HT_{2C} antagonism (clozapine, olanzapine, risperidone, quetiapine) Partial agonism of D_2-receptor and of 5-HT_{1A} (aripiprazole, ziprasidone)	Greater risk of weight gain and DM with clozapine and olanzapine Intermediate risk of weight gain and DM with risperidone and quetiapine Lower risk of weight gain and DM with aripiprazole and ziprasidone

DM, diabetes mellitus

through 5-hydroxytryptamine $(HT)_{2C}$ receptor antagonism or, in the case of aripiprazole, 5-HT_{1A} agonism [25]. However, SGAs may block receptors for other neurotransmitters in the brain (e.g. adrenergic α1, histamine H_1 and muscarinic receptors). As the use of SGAs increased, reports of substantial weight gain, new-onset or worsening diabetes and dyslipidaemia began to emerge [26].

Prevalence In individuals with mental health disorders, antipsychotics can elicit an almost twofold higher risk (vs placebo) of a clinically relevant weight gain (≥7%) [27]. The prevalence of diabetes is around 10% among individuals taking antipsychotics, two- to threefold higher than in an age-matched general population. A large meta-analysis of 438,245 people with severe mental health problems showed that the prevalence of diabetes prior to antipsychotic therapy averaged 2.9%, increasing to 11.3% among individuals receiving antipsychotic treatment. The higher diabetes prevalence was seen for all antipsychotics (first and second generation) except aripiprazole and amisulpride [28]. Randomised controlled trials and population observational studies have shown that the risk of developing diabetes differs markedly between the various compounds: higher risk for clozapine or olanzapine; intermediate risk for risperidone and quetiapine; lowest risk for aripiprazole, which has a different mode of action [28, 29].

Clinical presentation Substantial weight gain commonly occurs within a few weeks after SGA initiation and continues in the longer term albeit at a lower rate [27]. Unhealthy food choice and physical inactivity, in addition to possible disease-specific associated mechanisms, may contribute to obesity in people with severe mental health problems. Nevertheless, the use of antipsychotics, especially atypical ones, appears to be the most important factor related to weight gain.

A rapid rise in blood glucose and incidence of diabetes after SGA initiation is commonly observed, even before weight gain, thus suggesting a direct role of SGAs [30]. The pattern of hyperglycaemia resembles that seen in type 2 diabetes but progression is more rapid. However, reports of DKA after the initiation of SGAs suggest they exert a direct deleterious effect on pancreatic beta cells and insulin secretion [31].

Pathophysiology/mechanisms Antipsychotics are obesogenic, inducing weight gain through increased appetite and food intake [25, 32]. The weight gain induced by SGAs may be explained by their antagonistic action on 5-HT_{2C} receptors. Indeed, serotonin acts through 5-HT_{2C} receptors to stimulate anorexigenic proopiomelanocortin neurons and decrease appetite; this effect is blocked by SGAs. Additionally, inhibition of histamine H_1 receptors could also contribute [25]. Antipsychotics could also reduce energy expenditure via a sedative effect that reduces voluntary movements or via altered expression of uncoupling protein-1 (UCP-1) in brown AT [32].

Antipsychotics, mainly SGAs, increase the risk of metabolic abnormalities, including diabetes, the risk being closely related to the degree of weight gain [33]. However, the precise mechanisms involved in the development of diabetes require further elucidation. As recently reviewed [30, 34], antipsychotic-induced disturbances in whole-body glucose homeostasis may involve cellular insulin signalling, endogenous glucose production, glucose uptake and insulin secretion, thus implicating different key organs (liver, skeletal muscle and endocrine pancreas). The primary defect in insulin signalling appears to be a marked impairment of post-receptor IRS-1 phosphorylation. Downregulation of intracellular downstream biochemical pathways subsequently occurs [25].

As DKA only occurs in situations of profound insulin deficiency, the higher rate of DKA in individuals treated with SGAs implies that these drugs drastically reduce insulin secretion, at least in some individuals. This may occur through disruption of normal glucose-induced insulin secretion or may result from a direct toxic effect on the pancreatic beta cells [25]. SGA-induced insulin dysregulation, as shown with olanzapine, might be partly due to blockade of central and peripheral muscarinic M_3 receptors [35].

Medical surveillance and management It is crucial to implement measures to prevent diabetes, especially in individuals at high risk, and to screen for diabetes after the initiation of antipsychotics [31]. In at-risk individuals, choosing an antipsychotic without (or with minor) adverse metabolic effects is recommended. Choices include newer drugs such as aripiprazole or ziprasidone, or even first-generation antipsychotics (less severe metabolic disturbances, yet with neuroendocrine disturbances) [36]. Lifestyle advice should be given to minimise the risk of weight gain and diabetes (i.e. early contact with a dietitian and advice on exercise). Monitoring fasting blood glucose for 12 weeks after initiation of therapy and annually thereafter for individuals without diabetes is recommended [33]. Switching an individual with blood glucose abnormalities to an SGA that is not associated with the development of diabetes (see above) may be also considered [36]. Given the high prevalence of obesity, besides metformin, the use of glucose-lowering medications that cause weight loss, such as GLP-1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, may offer some advantages, although further dedicated studies are needed [32, 36]. GLP-1 receptor agonists were shown to reduce antipsychotic-associated body weight gain, particularly in clozapine/olanzapine-treated patients, an effect accompanied by improvement in fasting plasma glucose levels [37]. When severe insulin deficiency is present, especially in DKA, insulin therapy is necessary.

Antiretroviral therapy

Four classes of ART can be employed, in different combinations, to treat HIV infection: nucleoside analogue reverse transcriptase inhibitors (NRTIs); non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); and integrase strand transfer inhibitors (INSTIs) (Table 4) [38, 39]. The emergence of new classes of ART, and of new drugs in each class, not only improved the efficiency of HIV infection control but also reduced the metabolic side-effects of these molecules.

Prevalence The prevalence of ART-induced diabetes has evolved markedly during recent decades, mostly related to changes in usage of antiretroviral compounds. For instance, in France [40] and Denmark [41], there was a clear decrease in the incidence of diabetes after 2005, in parallel with the replacement of stavudine, didanosine and indinavir by newer and less-toxic antiretroviral compounds. In a recent meta-analysis, Nansseu et al [42] described marked differences in diabetes incidence in North America (19.1/1000 person-years of follow-up (PYFU)) and Europe (8.0/1000 PYFU). The global cumulative incidence averaged 4.9% worldwide, higher among Americans (6.1%) than Europeans (3.8%), reflecting variations in adiposity.

The main factors associated with ART-induced diabetes are older age, Black or Hispanic origin, family history of diabetes, being overweight or obese, central adiposity, dyslipidaemia, the metabolic syndrome, disturbances in fat distribution (lipoatrophy and/or lipohypertrophy), and type of ART. In low- and middle-income countries, some individuals with HIV have received, even recently, the toxic NRTIs stavudine, zidovudine and the PI indinavir, so that the prevalence of diabetes is relatively high. In South African individuals with HIV infection, the crude incidence of diabetes was 13.2/1000 PYFU, close to that observed in North America [43].

Clinical presentation Diabetes is generally asymptomatic in individuals with HIV infection, so diabetes screening should be done after ART initiation or modification. This is particularly important in those at risk for diabetes, considering their own or familial background, the presence of lipodystrophy and the composition of the ART regimen (Table 4) [38, 39].

Pathophysiology/mechanisms Lipoatrophy and disturbances in fat distribution are likely major drivers of insulin resistance in HIV-infected individuals, combining at different magnitudes a peripheral lipoatrophy and a central fat gain (visceral adiposity) [38, 39].

Table 4 ART and its impact on adiposity

Antiretroviral drug class	Drugs	Lipoatrophy	Peripheral fat gain	Central fat gain
NRTIs	Zidovudine	++		+
	Stavudine	+++		++
	Didanosine	±		±
	Lamivudine	0		0
	Abacavir	0		0
	Tenofovir	0		0
	Emtricitabine	0		0
NNRTIs	Efavirenz	±	±	+
	Nevirapine	0		0
	Etravirine			
	Rilpivirine	0	±	0
	Doravirine			
PIs	Indinavir	±		+
	Ritonavir	±		+
	Nelfinavir	±		+
	Lopinavir/ritonavir	±		+
	Atazanavir/ritonavir	0	+	++
	Darunavir/ritonavir	0	+	++
INSTIs	Raltegravir	0	+	++
	Dolutegravir	0	+	++
	Elvitegravir	0	+	+
	Bictegravir			

The information in this table is reproduced from [38, 39]

0, no effect; ±, mild induction; +, moderate induction; ++, strong induction

The major role played by the first-generation NRTIs stavudine and zidovudine in the occurrence of lipoatrophy (and trunk fat hypertrophy) has been clearly documented and is associated with AT macrophage infiltration and inflammation, mitochondrial toxicity and dysfunctional fat cells, including adipocyte insulin resistance [44]. Prior exposure to thymidine NRTIs could induce remaining fat damage and potential ART-induced fibrosis could impair AT expansion, leading to lipotoxicity and metabolic disturbances. It has been proposed that thymidine NRTIs promote irreversible mutations in mitochondrial DNA, leading to mitochondrial dysfunction and AT premature ageing [45, 46].

The role of PIs in the emergence of trunk fat hypertrophy is less clear [47]. Molecular analysis of subcutaneous AT from PI-treated individuals showed a reduced expression of the miRNA-processing enzyme DICER, associated with a downregulation in brown- and beige-specific AT genes such as *UCP1*, together with a shift towards a proinflammatory and pro-fibrotic state and limitation of fat storage and AT browning [39, 48]. In vitro studies have shown that some PIs inhibit the enzyme zinc metallopeptidase (ZMP)-STE24, which is mandatory for the maturation of the nuclear matrix protein prelamin-A into lamin-A. As a consequence, prelamin-A accumulation induces altered adipocyte function and insulin resistance, and promotes central fat redistribution [49].

The NNRTI efavirenz was shown in vitro to alter adipocyte development and function and increase inflammation, while nevirapine exerted beneficial effects [50].

The mechanisms by which INSTIs cause increased adiposity are poorly understood. However, we have shown that, in accordance with in vitro studies on human models using dolutegravir or raltegravir, subcutaneous and visceral AT from INSTI-treated macaques exhibited increased fibrosis, adipocyte size and adipogenic marker expression (*PPARG* and *CEBPA*) when compared with untreated animals [51].

Thus, some antiretroviral compounds (mainly first-generation NRTIs and PIs) favour adipocyte insulin resistance that increases the release of NEFA, which in turn results in lipotoxicity with subsequent insulin resistance in the liver, skeletal muscle and endothelium, and altered insulin secretion in the endocrine pancreas. Furthermore, besides the major impact of ART on insulin sensitivity, PIs were shown to alter beta cell function. Drugs including lopinavir, atazanavir and ritonavir can reduce the insulin-secretory properties of insulinoma cells and human pancreatic islets, and can increase beta cell apoptosis [52].

Medical surveillance and management Limited information is available about prevention or treatment strategies targeting metabolic dysfunction in HIV-infected individuals. It seems relevant to propose a strategy to prevent new cases of diabetes, diagnose existing diabetes, develop an effective plan to manage cardiovascular risk factors, and engage and retain patients in care [53].

The prevention and diagnosis of diabetes is crucial in HIV-infected individuals but there is no single laboratory test available that can diagnose insulin resistance (the most popular being HOMA-IR). HbA_{1c} may underestimate blood glucose levels in HIV-infected individuals, likely due to higher corpuscular volume and to the frequent use of the NRTI abacavir, and so must be interpreted cautiously [54]. Fasting plasma glucose should be screened every 6–12 months in all individuals treated for HIV, and also every 1–3 months following ART initiation [53]. Both lifestyle modifications (exercise and diet) and metformin improved symptoms of the metabolic syndrome in these individuals [55]. The avoidance of older ART associated with adiposopathy (lipoatrophy and central lipohypertrophy) is also warranted to prevent fat alterations.

In HIV-infected individuals with diabetes, management should follow classical guidelines [56]. Lifestyle modification remains a pillar of care. Metformin is the first-line medication and second-line treatments should be chosen after considering their respective advantages and disadvantages [54] and the patient's profile and preference. Because HIV-infected individuals are commonly overweight or obese, the choice of a medication that is neutral or beneficial in adiposity should be considered.

Immune checkpoint inhibitors

The cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1) and its ligand (programmed death-ligand-1 [PDL-1]) are immune checkpoint proteins that negatively regulate the immune response and thereby maintain self-tolerance. These proteins can be targeted by monoclonal antibodies (Table 5). In cancer treatment, ICIs lead to activation of the immune system, to overcome tumour-induced immunosuppression. However, ICIs can interfere with the physiological function of immune checkpoints to promote self-tolerance, thereby inducing a unique spectrum of immune-related adverse events. Various endocrinopathies

Table 5 ICIs able to trigger diabetes mellitus

ICI	Monoclonal antibodies	Risk of diabetes
CTLA-4 inhibitor	Ipilimumab	Lower[a]
PD-1 inhibitors	Pembrolizumab Nivolumab	Higher[b]
PDL-1 inhibitors	Atezolizumab Avelumab Durvalumab	Higher[b]

[a] Lower risk than with PD-1 or PDL-1 inhibitors

[b] Higher risk than with CTLA-4 inhibitor

have been reported, including new-onset diabetes that may, at least partly, resemble autoimmune type 1 diabetes [57–60].

Prevalence in clinical practice According to a meta-analysis of 40 trials among 24,596 individuals, specific ICI-related diabetes events are rare. However, compared with placebo or other therapeutic strategies, ICIs significantly increased the risk of serious hyperglycaemia (OR 2.41 [95% CI 1.52, 3.82]), diabetes (OR 3.54 [1.32, 9.51]), all-grade type 1 diabetes (OR 6.60 [2.51, 17.30]) and serious-grade type 1 diabetes (OR 6.50 [2.32, 18.17]) [61].

A retrospective study of data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) identified 735 cases of new-onset diabetes associated with ICIs between 1 January 2015 and 31 December 2019, with an estimated overall incidence of 1.27% [62]. Among the 735 cases, 183 (24.90%) had fulminant type 1 diabetes, 338 (45.99%) presented with DKA, 183 (24.90%) had life-threatening outcomes and 41 (5.58%) died. Of note, reporting of ICI-related diabetes consistently increased from early 2015 to late 2019 [62].

Compared with anti-PD1 or anti-PD-L1 therapy, individuals who were treated with anti-CTLA-4 agents were significantly less likely to develop diabetes [63]. According to the WHO's database of individual case safety reports, only 12 out of 283 cases (4.2%) with new-onset diabetes were treated with anti-CTLA-4 alone, while anti-PD-1 monotherapy accounted for 76% of all cases [64].

Clinical presentation ICI-associated diabetes often resembles type 1 diabetes in its pathophysiology and clinical manifestation [58, 59]. However, some individuals may present with type 2 diabetes or worsening hyperglycaemia in the setting of pre-existent dysglycaemia or diabetes [65]. The average age at presentation (60s) is much higher than for typical type 1 diabetes and there is a slight male predominance. Clinical presentation is diverse, ranging from asymptomatic hyperglycaemia or classical symptoms of diabetes (polyuria, polydipsia) to life-threatening DKA [66]. The time from ICI initiation to the diagnosis of diabetes also varies widely, ranging from a few days to several months [63]. The short time period of hyperglycaemia prior to diagnosis, confirmed by almost normal or only moderately elevated HbA_{1c} levels, suggests acute beta cell destruction, confirmed by markedly decreased C-peptide concentrations [60].

Imaging of the pancreas shows non-specific results; however, diffuse pancreatitis has been reported, more commonly with anti-CTLA-4 agents than with PD-1 inhibitors [67].

Pathophysiology/mechanisms ICI-mediated activation of the immune system is not restricted to antitumour activity; immunoreactivity can be triggered against normal tissues such as beta cells, with a result mimicking type 1 diabetes. The precise pathogenesis of this adverse event is not well understood. Early identification of individuals who may be prone to ICI-related diabetes development is vital, yet biomarkers have been poorly investigated [66]. It has been suggested that the presence of islet-cell antibodies (predominantly those targeting GAD) or susceptible HLA genotypes (e.g. DR4-DQ4) might be indicative of a higher risk, yet uncertainty remains [63, 68]. The association of low or even undetectable C-peptide concentrations concomitantly with relatively low HbA_{1c} levels is suggestive of a fulminant onset of diabetes. However, only about half of the individuals with ICI-related diabetes were positive for at least one islet antibody, with anti-GAD being the most common [58, 63].

The implication of PD-1/PD-L1 inhibitors in most ICI-induced diabetes cases highlights the crucial role of the PD-1/PD-L1 axis in mediating tolerance towards islet beta cells [68]. Animal data show that PD-1 engagement in immune cells is critical for attenuating antigen-specific T cell responses [68]. PD-L1 expression in the pancreas might also be indicative of an attempt to subdue an inflammatory response by engaging PD-1-expressing self-reactive T cells [68]. Besides the PD-1/PD-L1 axis, CTLA-4, a cell surface receptor, is also a negative regulator of T cell activation. However, CTLA-4 is not expressed in beta cells, possibly explaining why anti-CTLA-4 treatment rarely causes ICI-related diabetes in the absence of pancreatitis.

Pancreatic samples from individuals with ICI-induced diabetes are essential to understand the immune phenotype, yet they are still rare [68]. In an individual who developed type 1 diabetes following anti-CTLA-4 and anti-PD-1 combined therapy, pancreatic islets that were infiltrated by T lymphocytes had low levels of PD-L1 expression, suggested to be associated with beta cell damage [69].

Medical surveillance and management Prior to ICI initiation, individuals should be informed of the potential diabetes risk and receive education on the symptoms and signs of hyperglycaemia and DKA so that they can seek medical attention as soon as symptoms occur. Blood glucose and HbA_{1c} should also be checked routinely prior to ICI treatment and at regular follow-up intervals.

The management of ICI-related diabetes depends on the degree of hyperglycaemia and presence of DKA [60, 62]. In individuals with mild hyperglycaemia, ICI therapy may continue but close laboratory monitoring is recommended. In those with moderate hyperglycaemia, continuation of ICI therapy is feasible but insulin treatment should be initiated. For individuals with severe hyperglycaemia, and of course DKA, ICI treatment should be at least interrupted temporarily and insulin therapy becomes mandatory. After recovery, re-administration of ICIs may be considered but close glucose monitoring is essential. ICI-related diabetes is irreversible and

usually requires life-long insulin therapy. Thus, management should be multidisciplinary and include both endocrinologists and oncologists [63, 65].

Conclusion

Drug-induced hyperglycaemia is a growing concern, especially because of an increased use of older agents such as GCs or new medications (antipsychotics, ART, ICIs). It is uncertain whether this hyperglycaemia directly results from drug action or whether, in some (most?) instances, the medication simply unmasks pre-existing diabetes in individuals at high risk because of poor lifestyle habits. The exact mechanisms by which the implicated drugs cause hyperglycaemia and diabetes remain to be further investigated but appear to be multiple (targeting insulin secretion/sensitivity), different between pharmacological classes, and potentially complex. For some pharmacological classes, weight gain and/or AT dysfunction (adiposopathy) certainly play a role in the development of diabetes.

Despite potential new-onset or worsening diabetes, the benefits of appropriately prescribed treatment with the four pharmacological classes of drugs discussed in the present review largely outweigh the potential risks of discontinuing therapy (as for statins). Nevertheless, clinicians should be mindful of the risk of deterioration of glucose homeostasis, especially in individuals with pre-existing risk factors, so that alternative therapies with a lower risk of hyperglycaemia may be chosen whenever possible. Careful monitoring is recommended for high-risk individuals receiving agents known to impair glucose tolerance, with the goal of preventing diabetes or initiating early treatment and avoiding diabetes-associated complications. Lifestyle intensification remains a key step to prevent or treat drug-induced disturbances in glucose homeostasis; if insufficient, metformin remains the first-choice medication. Newer glucose-lowering agents that may promote weight loss are of potential interest in the treatment of individuals whose diabetes occurs in a context of weight gain and insulin resistance. For severe hyperglycaemia and of course DKA, a marker of profound beta cell dysfunction, insulin therapy becomes mandatory and should be adjusted according to close blood glucose monitoring.

Supplementary Information The online version contains a slide of the figure for download, which is available at https://doi.org/10.1007/s00125-022-05666-w.

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